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10/572,974	03/22/2006	Stacey Ann Jones	PR60397USw	4587
23347	7590	06/11/2009	EXAMINER	
GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY, MAI B482 FIVE MOORE DR., PO BOX 13398 RESEARCH TRIANGLE PARK, NC 27709-3398			PAGONAKIS, ANNA	
			ART UNIT	PAPER NUMBER
			1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/572,974	Applicant(s) JONES ET AL.	
	Examiner ANNA PAGONAKIS	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 February 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) 1-3, 7 and 11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4-6, 8, 10 and 12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3 sheets, 3/22/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicant's election of Group II, claims 4-6, 8, 10 and 12 in the reply filed on 2/26/2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-12 are pending in the application. Claims 1-3, 7 and 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim.

Claims 4-6, 8, 10 and 12 are currently under examination and the subject of this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4-6, 8, 10 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as their invention.

The use of the designation FXR renders the claims indefinite as the recitation is too vague. FXR is a simple acronym/abbreviation that has many different meanings in the art and thus the inclusion thereof renders the claims indefinite.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-6, 8, 10 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 4 recites the administration of a "therapeutically effective amount" of an FXR agonist.

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This limitation is indefinite because it is not clear what the amount being administered is effective for. The preamble of the claim is not linked to the body of the claim in such a way as to clearly convey which condition/disease the therapeutically effective amount is administered for. The phrase "therapeutically effective amount" being administered has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art.

Claims 4-6, 8, 10 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 4 recites the administration of an "FXR agonist." This limitation is indefinite because it is not clear what the breadth of the agonist is drawn to. It is unclear whether the FXR agonist is a metal, nucleic acid, protein, surfactant etc. The claim is solely drawn to a functional characteristic and there is no disclosed correlation between structures and function.

Claims 4, 8, 10 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Present claims 4, 8, 10 and 12 are directed to a method of reducing or preventing development of liver fibrosis comprising administering to a mammalian subject in need of such treatment a therapeutically effective amount of an FXR agonist.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP 2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1159, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds

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that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, “not a mere wish or plain for obtaining the claimed invention.” *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office (“PTO”) Guidelines for Examination of Patent Applications under 35 U.S.C. 112.1 “Written Description” Requirement (“Guidelines”), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by “showing that an invention is complete by disclosure sufficiently detailed, relevant identifying characteristics,” including, inter alia, “functional characteristics when coupled with a known or disclosed correlation between function and structure...” *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicant has failed to provide any structural characteristics or chemical formulas aside from the express identification of FXR agonist per se, that would provide adequate written description of the genus of compound capable of behaving as an FXR agonist that Applicant was actually in possession of, and intended to be used within the context of the present invention, at the time of the present invention. For the purposes of this invention, the use of the term 'FXR agonist' will also be understood to encompass all compounds that behave as FXR agonists as well as precursors and other compounds that mimic FXR agonist activity. Applicant has failed to provide any limiting definition, let alone an exemplary definition, or any chemical or physical characteristic of these compounds such that one of ordinary skill in the art would have been able to readily identify the scope of those compounds encompassed by the term "FXR agonist."

MPEP 2163 recites, “The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice,

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reduction to drawings, or by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the claimed genus." Please reference *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-6, 8, 10 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by “undue experimentation,” the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

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The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,
- 3) the presence or absence of working examples,
- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art,
- 7) the predictability of the art, and
- 8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to a method of reducing or preventing development of liver fibrosis comprising administering to a mammalian subject in need of such treatment a therapeutically effective amount of an FXR agonist.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

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That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

The art of treating and preventing hepatic fibrosis is inherently unpredictable due to the diverse chromosomal, genetic, and protein changes associated with progression of hepatic fibrosis as well as a poor understanding of what environmental, genetic, and biological factors are involved in hepatic fibrosis development.

2. The breadth of the claims

The claims are extremely broad insofar as they disclose the general treatment and prevention of hepatic fibrosis, regardless of the underlying primary cause of such cancer.

3. The amount of direction or guidance provided and the presence or absence of working examples

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The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to *prevent* hepatic fibrosis, particularly in humans. Further, there is no working example whereby animals or humans predisposed to developing hepatic fibrosis are prevented from developing such a condition simply by administration of the claimed compound.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed compounds could be predictably used as a treatment or prevention of hepatic fibrosis as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

The prevention of fibrosis is entirely unpredictable due the diverse environmental, genetic, and biological causes of hepatic fibrosis. Further still, there is limited evidence in the prior art that compounds useful in treating hepatic fibrosis are also effective in preventing the same fibrosis they treat.

Determining if any particular claimed compound would *prevent* hepatic fibrosis would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants.

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Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 4-6, 8 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Kliewer et al. (U.S. 2003/0203939 A1).

Kliewer et al. teach the use of GW4064 for the treatment and prevention of hepatic injury (abstract and paragraph [0015]). The claims administer the elected compound to a patient for the prevention of liver fibrosis. In order to prevent one must necessarily administer before the presence of disease and therefore the administration of the elected to the patients according to Kliewer et al. inherently prevents the claimed diseases.

It is noted that the specification on page 4 alternatively identifies the elected compound as GW4064.

Claims 4-6, 8 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Jones et al. (U.S. 2005/0107475). The claims administer the elected compound to a patient for the prevention of liver fibrosis. In order to prevent one must necessarily administer before the presence of disease and therefore

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the administration of the elected to the patients according to Jones et al. inherently prevents the claimed diseases.

Jones et al. teach the use of GW4064 for treatment of obesity (abstract and paragraph [0021]).

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Patricia A. Duffy/
Primary Examiner, Art Unit 1645

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